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PELLAGRA.

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Definition. Pellagra is a specific disease of man characterized by clinical manifestations on the part of the digestive tract, the nervous system and the skin. The digestive tract presents various grades of inflammation. The nervous system manifests varying grades of toxic reaction, ranging from peripheral neuritis to toxic psychosis, or the lethal central neuritis. The cutaneous eruption is the most characteristic feature of pellagra. It is a symmetrical erythema involving especially the backs of the hands, and it has the same importance in the diagnosis of pellagra as has the eruption of measles or of smallpox in the diagnosis of those diseases.

Etiology. *Specific Causation.* The specific cause of pellagra is unknown. There are numerous theories championed by one or more students of the disease, some of them definite, others quite nebulous. Roussel, in 1866, presented the zeistic theory in such definite form and supported it by such clearly marshalled facts that from his day until 1905 this conception of pellagra remained almost unchallenged. According to Roussel, pellagra is due to two factors or groups of factors, of which one is external and the other resides within the human body itself. The extrinsic factor is altered maize, which is the special and specific cause of pellagra, giving to the disease its character as a pathologic entity and without which the other etiologic factors are powerless to produce this malady. However, in order to be effective, the altered maize is not alone sufficient,

since observation proves that its abundant use often fails to produce pellagra; it requires in addition to encounter within the body of the victim certain conditions of vitality, just as parasites need to encounter appropriate susceptible hosts and as seeds require suitable soil for their development. All causes of enfeeblement, particularly the phases of sexual activity in the female and above all the factor of heredity, create this necessary vital condition of susceptibility. Such, says Roussel, is the dual basis indispensible as a solid foundation for the etiologic theory of pellagra. Much in this view of Roussel still merits admiration and respectful consideration. In 1905 Sambon launched a most effective attack against the maize theory, and it is now almost universally recognized that pellagra occurs in those who do not eat maize, the possibility of which was absolutely denied by Roussel in his time. Sambon, unfortunately, coupled with his refutation of the maize theory the thesis that pellagra is an insect-borne infectious disease, transmitted by a fly of the genus Simulium, a theory which has not been able to survive in the subsequent study of pellagra.

In 1911 the Illinois State Pellagra Commission, after extensive studies of outbreaks of pellagra in institutions for the insane over a period of two years, drew the following conclusions:

1. According to the weight of evidence pellagra is a disease due to infection with a living microörganism of unknown nature.
2. A possible location for this infection is in the intestinal tract.
3. Deficient animal protein in the diet may constitute a predisposing factor in the contraction of the disease.

This commission recommended an increase in the animal protein of the dietaries of the state hospitals and advised compulsory notification of all cases of pellagra. The Robert M. Thompson Pellagra Commission, after extensive study of pellagra in the general civilian population of the Southern United States and in the West Indies, in the course of which particular attention was given to the maize theory and to Sambon's theory of insect transmission, has come to conclusions supporting the Illinois Commission. Jobling and Peterson and their co-workers, as a result of their extensive epidemiologic studies in Nashville and vicinity, also incline to the same view.

Sandwith, in 1912, raised the question whether pellagra might not be a disease essentially due to a deficiency of nutrition, and he pointed out certain analogies between pellagra and beriberi. This theory has been enthusiastically supported by Funk and by Goldberger and their followers. Particularly striking evidence in favor of this theory is found in the elimination of pellagra from eleemosynary institutions by radical improvement of the dietary. That such results admit of another interpretation is evident, as was pointed out by the Illinois Commission in 1911. In November, 1916, Goldberger and Wheeler announced the experimental production,

by means of a deficient unbalanced diet, of a "typical" eruption justifying a diagnosis of pellagra in six of eleven human subjects experimented upon. Because of the official position of these authors this definite and positive announcement, although a mere preliminary communication unaccompanied by detailed facts and illustrations, received wide recognition as a real and valid discovery. The full report, which has now appeared after a delay of more than three years, reveals that what the authors at first designated as a "typical" eruption was actually a dermatitis on the scrotum and apparently on the opposed surfaces of the thighs also in some of the individuals. Apparently the authors no longer wish to maintain that this is a "typical" eruption justifying the diagnosis of pellagra, for in the full report they avoid this expression, and furthermore even express a doubt as to whether their experimental diet was of the specific quality necessary to cause the usual eruption of pellagra. Sullivan made a biologic study of the diet employed by Goldberger and Wheeler, and with it he induced polyneuritis and paralysis in experimental animals, which condition he was able to prevent and even to relieve after its development by the administration of extracts of rice polishings. McCollum, who with his collaborators has carried out an extensive series of studies upon diets of this type, has finally expressed his conviction that pellagra is an infectious disease.

Perhaps the most serious difficulty for the deficiency theory has arisen during the period of the recent war. Dietary deficiency became the rule in central Europe and the resulting increase in debility and in death-rate have been conspicuously reported. Among the diseases increased in this part of Europe during the period of deficient diet, pellagra is conspicuously absent. Actually there was observed an extensive outbreak of pellagra in a British camp for Turkish prisoners of war located in Egypt. Many of these prisoners had evidently been pellagrins before capture, but the disease also spread to new victims in the prison camp. This outbreak of pellagra was investigated by a British Committee of Inquiry, and they ascribed it to the relatively deficient diet of the Turkish prisoners, contrasting, in their report, their condition with that of the German prisoners in an adjacent camp, men who had subsisted on a most excellent diet before capture and who were receiving as prisoners a diet above reproach. Enright has since reported an extensive outbreak of pellagra in this very camp of German prisoners, the outbreak having begun at almost the exact time that the above-mentioned Committee of Inquiry had completed its investigations, namely, December, 1918, and January, 1919. Enright concludes, "Although I have been unable to advance any satisfactory cause for this mysterious outbreak of pellagra, I do submit that I have established a clear case against a 'food deficiency' as being the only factor involved."

In my own opinion the etiology of pellagra depends upon two factors analogous to those recognized by Roussel: (1) The specific causative factor which is a living organism, an infectious agent derived directly or indirectly from a previous case of the disease, and (2) a factor or group of factors, quite non-specific, which serve to reduce the resistance of the victim. In this latter group are recognized malnutrition, either from inadequate food or inability to utilize food in an adequate manner, cachexia of disease, overwork, depressing influence of hot weather, strain of reproduction in women, involution of old age, alcoholism and many other such influences. The specific causative factor, which I believe to be a living organism, remains unrecognized. Most probably it resides in the gastro-intestinal tract, and the absorption of its products from the digestive tract gives rise to the distant manifestations of pellagra. In regard to the factors influencing the possible transmission of the hypothetical parasite, as well as those which may influence the resistance of the human individual, a great many facts have become established by epidemiologic studies in pellagrous districts, some of which are next to be considered.

Geographical Location. Isolated cases of pellagra are occasionally observed in various parts of the world. In view of the chronic and recurrent nature of the disease and the extent of modern travel, such observations are to be expected. In general, however, the relationship between place and origin of pellagra is one of the most striking features of the disease. Pellagra is contracted where there is a preëxisting case of the disease. Its apparent sporadic origin is so rare as to warrant a grave doubt as to the accuracy of diagnosis or the adequate search for preëxisting cases in such instances. Of the thousands of children suffering from malnutrition and lack of food seen every year in the hospitals and clinics of large cities outside pellagra districts, none suffer from pellagra. In pellagrous districts, on the other hand, a very considerable proportion of persons, and especially the children, suffering from lack of food, diseases associated with malnutrition or other depressing conditions, contract pellagra.

Pellagra is prevalent in certain parts of Turkey, Egypt, Roumania, Austrian Tyrol, Northern Italy, West Indies, Yucatan and the Southern United States. Outbreaks have been reported in South Africa and in the Malay States. Outbreaks of considerable importance and sometimes persisting for several years have been observed in the Northern United States, especially in institutions for the insane. In the geographic areas where the disease prevails its distribution is extremely uneven.

Even in the small communities where pellagra is most prevalent the degree of proximity to a pellagrin shows a significant relationship to the danger of contracting the disease. Thus the Thompson-McFadden Commission, in 1913, observed a pellagra incidence of

6.59 per cent. among persons living in the same house with a pellagrin, 1.72 per cent. among persons living next door to such a house and 0.52 per cent. for those living farther away than next door but in the same village communities. This house relationship of pellagra has been confirmed by the subsequent third report of the same commission and also by the independent work of Jobling and Peterson.

Race, Age and Sex. The relationship of race to pellagra is apparently in part directly dependent upon racial variation in resistance to the disease, but in part indirect because one race may be relatively segregated, may be less prosperous or may live upon poorer food. In Spartanburg County, South Carolina, up to October 15, 1914, the negro population of 28,507 had shown 153 recorded pellagrins, an incidence rate of 54 per 10,000, whereas the white population of 62,119 had shown 1027 recorded pellagrins, an incidence rate of 165 per 10,000. This lower incidence in negroes occurred in conjunction with greater poverty of this race and a diet poorer in quality, quantity and variety. The negro population was for the most part relatively segregated from the white race, and thus from the white pellagrins and the incidence of pellagra in the negroes was lowest in those sex and age groups most completely segregated in this way. Although much less frequently attacked by pellagra, the negroes when attacked suffered most severely. Of the 153 cases in negroes, 64, or 41.8 per cent., terminated in death in the first year of the disease, whereas in the white race the analogous death-rate was only 12 per cent. The higher death-rate may express a lower racial resistence to pellagra, but, in part at least, it would seem to be correlated with the greater poverty and the poorer diet of the negro race. No less than 113 of the 153 negro cases occurred in females over sixteen years of age, namely, that portion of the negro race which is least effectively segregated from the white race.

The age at onset of pellagra in each race and sex in the Spartanburg statistics is indicated in Figs. 1, 2 and 3. It is evident that white women and children, older white men and negro women furnished the bulk of the cases. Pellagra is rare in the first year of life, fairly prevalent in white children under ten years of age, distinctly less prevalent at about the age of puberty, again increasing to maximum frequency in women in the age period sixteen to forty-five years, but remaining infrequent in men until after the thirty-second year. The greater prevalence in women during the active period of life is a most remarkable feature. The occurrence of pellagra in children of any district is a feature which stamps the district as an endemic focus of the disease.

The death-rate from pellagra in the initial attack is lowest in children and relatively quite low in women in the age period sixteen to forty-five years, indicating that the factors which bring about an attack of the disease are not identical with the factors which determine a fatal outcome of the attack. In children, pellagra would

appear to present no more serious danger than measles, while in both men and women more than fifty years of age the death-rate is well above 20 per cent. in the first year.

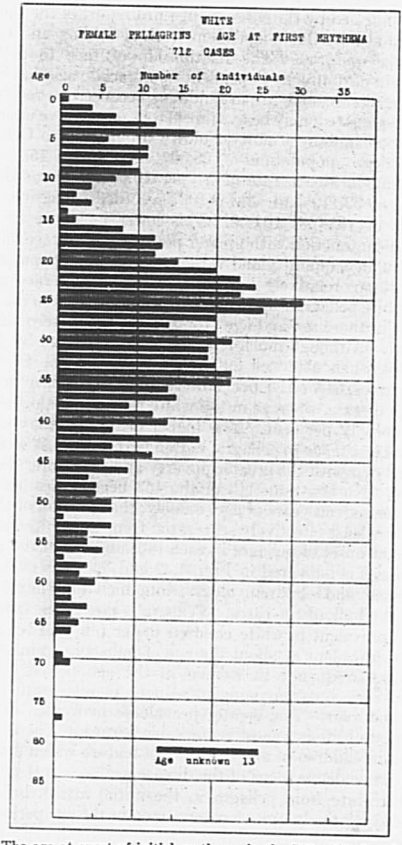

FIG. 1.—The age at onset of initial erythema in the 712 white female pellagrins of the Spartanburg County series. The age distribution is shown for 699 cases. In 13 cases the age was not ascertained. The small number of initial attacks from the eleventh to the sixteenth year is remarkable. (After Siler, Garrison and MacNeal.)

Relation to Food. The older theories assumed that pellagra is due to the toxic action of maize in the diet. It is undoubtedly true

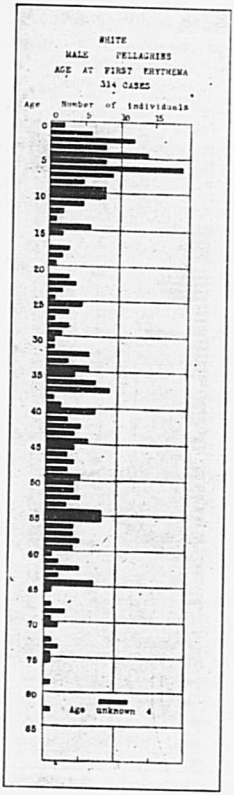

FIG. 2.—The age at onset of initial erythema in the 314 white male pellagrins of the Spartanburg County series. The age distribution is shown for 310 cases. In 4 cases the age was not ascertained. (After Siler, Garrison and MacNeal.)

that the vast majority of pellagrins have eaten maize or maize products, but feeding experiments with and without maize in

endemic foci of pellagra have failed to reveal any greater incidence of pellagra in those taking the large quantities of maize. Further-

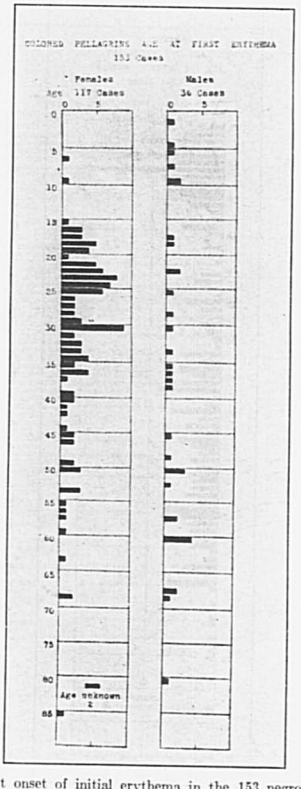

FIG. 3.—The age at onset of initial erythema in the 153 negro pellagrins of the Spartanburg County series. (After Siler, Garrison and MacNeal.)

more, the prophylactic exclusion of maize from the diet of pellagrous families has proved to be a failure, for under these circumstances there have been observed not only recurrences of the disease in those

already affected but also the outbreak of new cases in other members of the family. Perhaps even more convincing has been the report of Stannus of pellagra in prisoners who had had no maize for years, and of Viswalingham, who observed an outbreak of pellagra in Chinese coolies whose diet contained rice as the principal element and contained no maize. The Thompson-McFadden Commission, in 1913, failed to find a positive correlation between the frequency of use of any single food and the frequency of occurrence of pellagra. At present it would seem that no one seriously maintains that pellagra is caused by any single food. There remains, however, the possibility that the excessive use of certain foods, maize for example, may predispose to the development of the disease or render the attack more severe.

A second possibility is that the absence or insufficiency of certain dietary elements, rather than the excess of a certain element, may bear an etiologic relation to pellagra. The pellagra-preventing value of animal foods, especially milk, emphasized by the Illinois Commission and clearly demonstrated by the Thompson-McFadden Commission, is now generally recognized. Recently even Goldberger and his colleagues of the Public Health Service (1920) seem to have abandoned the advocacy of beans in favor of milk, milk products and fresh meat as preventive diet for pellagra. In my own opinion the relative pellagra-preventing value of these foods is similar to their value in preventing tuberculosis. They bring about improved nutrition and increased resistance to the specific cause of the disease. That the mere lack of animal foods is not the specific cause of pellagra is shown by the host of strict vegetarians who escape the disease. Furthermore, a relatively brief study in a pellagrous district suffices to disclose pellagrins who have taken milk daily all their lives, particularly young children, and occasionally one finds adult pellagrins who have eaten meat every day for years.

There remains a third possibility, namely, that general insufficiency of food may play an etiologic role. The theory that such insufficiency may be the specific cause of pellagra has already been discussed and rejected. There can be no question, however, that adequate nutrition is a most important factor of insurance against pellagra and in bringing about recovery from it, and that inadequate nutrition is a most important factor in predisposing to the development of pellagra in those who are exposed to the essential cause by residence in pellagrous districts.

Sanitary Disposal of Sewage. The association of poor sanitation with pellagra prevalence has been mentioned by many authors. The Thompson-McFadden Commission (1913) emphasized the fact that pellagra originates where insanitary surface privies are used and much less frequently where sanitary water-carriage systems of sewage disposal are properly employed. Such a relationship might

be explained by assuming that better sanitation increases the resistance to disease in general or that it operates by preventing the transfer of the specific cause of pellagra from the digestive tract of one person to another. An experimental test of this latter hypothesis was undertaken at Spartan Mills, S. C., in 1913, and the observations were carried through to August, 1916. Following, and apparently as a result of the installation of the sewer system, new cases of pellagra practically ceased to originate in the population of this village, whereas the old cases continued to suffer recurrences of pellagra about as would have been expected had no change in sanitation been undertaken. This relationship of sanitation to pellagra has been confirmed by the studies of Jobling and Peterson. The experiment at Spartan Mills has recently been attacked by Goldberger and Wheeler (1920), who state that they recorded 37 first-attack cases in Spartan Mills Village in 1917 (a year in which the original investigators were unable to continue their observations). The data to support this statement are referred to as "unpublished."

Experimental Inoculation.—Up to the present time the attempts to produce pellagra by experimental inoculation have failed in every instance to yield a conclusive positive result.

Clinical Manifestations and Course.

Introduction. Strambio described the signs and symptoms of pellagra in three stages of the disease. Roussel, although he did not follow Strambio's classification, nevertheless recognized three stages, not well separated from each other, which he designated as (1) commencing pellagra, (2) confirmed pellagra and (3) pellagrous cachexia. It seems to me preferable to regard pellagra as essentially a chronic disease presenting periods of activity and periods of quiescence, both of somewhat variable duration. According to this conception pellagra may best be studied clinically in two phases: (1) The period of active attack and (2) the interval between attacks. In the former period one may recognize a prodromal stage, an erythematous stage, a stage of hyperkeratosis and desquamation and a stage of sequelæ and convalescence. In the interval between attacks a great many various manifestations may be presented, some of them doubtless due to pellagra, but many of them depending upon quite other factors. The decision concerning the relative importance of pellagra and of other complicating disorders during this interval presents very great and often insuperable difficulties.

The Initial Active Attack. *Prodromal Period.* Pellagra sometimes begins suddenly with a cutaneous erythema as the first evidence of illness. More frequently there is a prodromal period varying from a few days to several months in length, during which

the patient is aware of diminished physical vigor; lessened appetite or distaste for particular foods or for all food, a burning sensation in the mouth and epigastrium, on the palms of the hands and the soles of the feet; attacks of vertigo, sometimes actual falling to the ground; depression of mind and spirit, evidenced by sadness and tardiness in thought, speech and action; pains in various parts of the body, especially headache, backache, pain and tenderness along the peripheral nerve trunks. Objectively there is often loss of weight, sometimes considerable; in women scanty or suppressed menstruation. Not infrequently there is diarrhea, more or less severe, but in many cases a persistent constipation or no evident disturbance of defecation. Reddening of the mucous membrane of the mouth and pharynx often accompany the burning sensation. Salivation is sometimes present. In patients carefully observed during this period one may occasionally detect an evanescent prelude erythema, first described by Merk. This eruption consists of numerous discrete red macules gradually fading into the surrounding skin, not raised above the skin surface and completely obliterated by slight pressure. It appears on the backs of the hands and forearms and may persist from a few hours to two or three days. This prelude erythema is probably not rare, but it is rarely observed. Pellagrin 597 of the Spartanburg series presented such a transient erythema on May 3, 1913, which disappeared in forty-eight hours and was followed by a frank and definite pellagrous eruption in June of the same year.

None of these prodromal symptoms or signs is sufficiently characteristic to warrant a certain diagnosis of pellagra, but the presence of many of them combined in the same individual in a pellagrous district is strong presumptive evidence of an impending attack of this disease, especially when a careful examination of the patient fails to reveal any other explanation of the observed manifestations. Even after the characteristic, diagnostic eruption subsequently appears, one is still left in doubt as to the relative importance of pellagra and of other complicating or predisposing factors in the causation of these interesting prodromal signs and symptoms.

The Stage of Active Eruption. The typical pellagrous eruption appears suddenly, ordinarily overnight, as a diffuse erythema or as separate red macules quickly becoming confluent, on the knuckles, dorsal surfaces of the phalanges and hands, gradually extending onto the wrists and forearms. At the same time or subsequently an eruption of similar character may appear elsewhere, especially on the forearms, the dorsal surfaces of the feet, the face, back of the neck, sternal region, upper arms, legs, perineum, scrotum, axilla and very rarely on the palms of the hands and the soles of the feet. Merk, who has presented the best clinical study of the cutaneous manifestations of pellagra, considers these eruptions in unusual locations, which he designated as "*atypische*," to be of no significance

for the diagnosis in the absence of the typical eruption on the backs of the hands.

The typical erythema is due to hyperemia, which causes not only redness but also swelling of the area above the level of the adjacent skin. The small flat areas, "fields," of the skin become more prominent while the furrows between the fields become deeper. As a rule the erythema becomes confluent within a few hours and then slowly extends, with a rather sharply demarcated margin. During this stage of progressive erythema the skin is very sensitive to external irritants, such as sunlight or even contact with the air. The sensation is that of burning. Itching may be complained of, but there is never any sign of scratching.

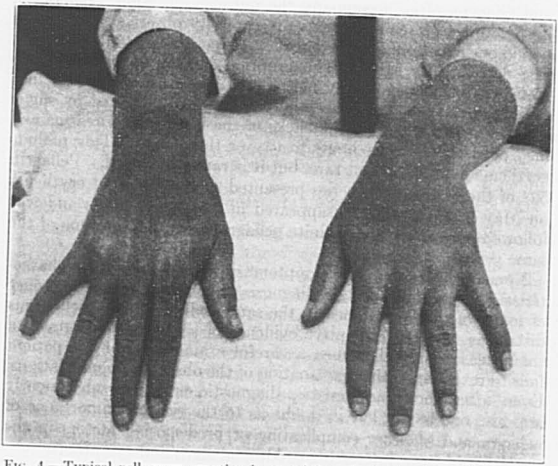

FIG. 4.—Typical pellagrous eruption in an adult male, in the stage of progressive erythema. (Photograph of the Thompson Pellagra Commission.)

Within the first few days the erythematous area begins to show increased desquamation in the form of fine scales, and in from one to two weeks the thickening of the horny layer of the skin with continuing desquamation obscures the underlying erythema. This hyperkeratosis becomes the most characteristic feature of the eruption during the greater part of its course. Thickening of the epidermis and desquamation continue for a variable period, two weeks to several months, usually about four weeks. In brunettes increased pigmentation also appears and is sometimes a marked feature of the erythematous area. Eventually the eruption tends

to disappear, the desquamation exposing a thin, parchment-like, smooth epidermis, more translucent than normal, with a pink, somewhat hyperemic dermis beneath. This restitution begins at the older parts of the lesion and gradually extends, so that the margins of the eruption persist longest. Indeed, in some patients one may observe at the same moment a narrow marginal zone of red, slowly advancing onto healthy skin, followed by a somewhat broader zone of deeply pigmented hyperkeratosis, this in turn succeeded by a still more extensive rough, scaly zone of desquamation, leading over into an area of atrophic smooth skin, where the eruption has completed its course. Occasionally one sees a new outbreak of erythema on the backs of the hands while there still remains the pigmented desquamating margin of a previous eruption on the upper forearms.

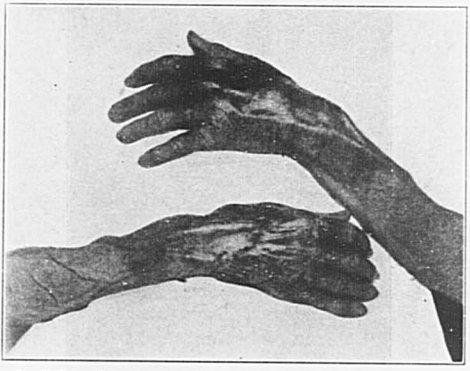

FIG. 5.—Pellagra in an emaciated woman, in the stage of hyperkeratosis and desquamation. (Photograph of the Thompson Pellagra Commission.)

The cutaneous eruption thus presents a variety of pictures in its various stages of evolution. In most cases the appearance is so characteristic that a reliable diagnosis may be made from a single observation. The subsequent developmental course of the eruption furnishes decisive evidence in most of the doubtful cases. In differential diagnosis one may have to consider trichophytoses and other forms of dermatitis due to local infection. These have undoubtedly been mistaken for pellagra at times, as recorded by Roussel. Their localization is hardly ever that of the typical eruption of pellagra. Sunburn may simulate the early stage of pellagrous erythema, but may be distinguished by its regular and

more rapid evolution. Scaly eruptions, which are occasionally observed on the forearms and shins of emaciated or cachectic individuals, may mislead the observer for a time. As a rule, however, the localization as well as the evolution of such eruptions will enable one to differentiate them from the eruption of pellagra.

The manifestations on the part of the digestive tract are variable in character, less constant in occurrence and far less reliable criteria for diagnosis than the cutaneous phenomena. Inflammation of the

FIG. 6.—Pellagra in a young woman in the stage of hyperkeratosis and desquamation. Emaciation is not evident. (Photograph of the Thompson Pellagra Commission.)

mucous membrane of the mouth and pharynx may precede, accompany or follow after the skin eruption. In degree this inflammation may vary from a slight reddening to a condition in which the entire visible mucous membrane is covered with a fibrinous exudate. Intense salivation is an occasional feature. Chronic pellagrins often present an irregularly swollen and fissured tongue. Swallowing may be so painful as to cause the patient to refuse solid food.

A burning sensation in the epigastrium, the pyrosis of pellagra,

is a fairly constant feature. It may precede the cutaneous eruption. Loss of appetite and actual distaste for food are frequently observed, nausea and vomiting only occasionally. In children, diarrhea usually precedes the eruption. In adults, particularly in women and in old men, diarrhea may be absent or may appear only late in the attack. Even in these patients, however, it may become a most alarming feature, the patient passing ten to thirty stools every

FIG. 7.—Pellagra in a child. The legs and feet show extensive eruption (Photograph of the Thompson Pellagra Commission.)

twenty-four hours for several days, with rapidly progressive emaciation and eventual lethal exhaustion. The stools possess a pronounced foul odor, often contain an excess of mucus and sometimes blood. Rectal examination frequently reveals a reddened mucous membrane resembling the redness of the mouth and pharynx. The alimentary disturbances may accompany the skin eruption or may appear, persist or disappear in a way quite independent of the latter. At times an exacerbation of the skin lesions is associated with an

improvement in the alimentary symptoms, and *vice versa*. This is probably mere accident, but some patients state that they always feel better when the eruption has appeared on the hands.

Nervous and mental disturbances are very rare in children but rather common in adults. Symptomatic depression is a frequent early manifestation. Vertigo and actual falling from loss of equilibrium are emphasized as early symptoms by Roussel. In the United States, Singer has found vertigo a prominent early symptom in six of eighteen severe cases. The more pronounced and characteristic nervous manifestations may be considered under two headings, (1) the so-called pellagrous insanity and (2) a peripheral neuritis.

The mental disturbance is either a frank toxic psychosis or one of the usual types of mental disorder varying according to the psychologic make-up of the individual, evidently precipitated by a toxic influence. Mental disturbance is observed in about 40 per cent. of all cases of pellagra, most frequently in women in the age period forty-one to sixty years and in men in the age period twenty-one to forty years. Children are practically exempt. Singer found that about 95 per cent. of the mental disorders appear to be the direct result of the pellagrous intoxication, corresponding to similar mental disturbances in other diseases and not properly to be classed as insanity. Symptomatic depression is the most frequent mental change, and it has been designated as the neurasthenic type. The attitude is that of a more or less hopeless sadness, with a lowering of tone, energy and attention, varying to melancholia, sometimes of a religious type, occasionally with suicidal tendency, to clouding of perception, sense falsifications, stupor and, in the most severe cases, to a syndrome of central neuritis leading to death. In other instances the picture is that of delirium, not essentially different from that of typhoid fever or of pneumonia. In most instances the depression or delirium clears up as the other manifestations of pellagra disappear and physical strength is regained. In about 5 per cent. of the mental cases Singer found a picture corresponding to one or the other of the well-known types of mental disorder, such as manic-depressive, hysteric, dementia precox type or senile dementia. In these cases the attack of pellagra appears to serve as the precipitating cause, which brings out a mental disorder already existing in the patient. During the active pellagrous attack the type of mental disorder may be masked by depression or delirium, but as recovery from pellagra takes place the characteristic features of the individual's preëxisting psychosis become clearly evident. Such patients present actual insanity, but the causation of it is not properly ascribed to pellagra. It would seem, however, that individuals of faulty nervous organization are relatively predisposed to pellagra and that an attack of pellagra tends to make evident the defective nervous organization

of such individuals. Chronic insanity due to pellagra itself, if it occurs at all, is rare.

The peripheral neuritis most frequently manifests itself as a paresis or paralysis of the muscles of the lower extremities. This occurs in children as well as in adults, but is not at all common and may really be due to some accompanying or complicating disease. It resembles an alcoholic neuritis and has been diagnosed as such in some cases. Possibly continued large doses of arsenic may occasionally bear a causal relation to the neuritis.

The temperature is characteristically subnormal in pellagra, varying from 35.5° to 37° C. Frequently it rises rapidly to 39° C. or even higher in the two or three days preceding death.

The pulse-rate is usually high in relation to the temperature and the pulse frequency usually increases sharply along with exacerbation of the other symptoms. The blood-pressure is low.

Duration of the Attack. The usual mild attack of pellagra lasts about four weeks from the appearance of the erythema until the manifestations are no longer evident. In some instances a second attack may supervene before the eruption of the first has entirely vanished, or, without intermission, the hyperkeratosis and desquamation may continue unabated for several weeks or months in exceptional cases. There is a very evident tendency to self-limitation of the attack, but the course and duration are subject to considerable variation and appear to be influenced to some extent by rest, careful feeding and nursing and especially by a diminution in the temperature of the atmosphere. Cooler weather or removal to a cooler climate stands out as perhaps the most definite factor in cutting short the pellagrous attack.

TABLE I.—DISTRIBUTION OF DEATHS IN THE FIRST ATTACK OF PELLAGRA ACCORDING TO YEAR OF ONSET IN SPARTANBURG COUNTY, SOUTH CAROLINA.

Year.	Before 1908.	1908.	1909.	1910.	1911.	1912.	1913.	1914.	Total.
Incident cases . .	57	20	57	141	234	211	251	209	1180
Deaths	13	2	16	28	33	27	38	30	187
Death-rate per cent.	22.8	10.0	28.1	19.9	14.1	12.8	15.1	14.4	15.8

Death-rate. The death-rate in the first attack in the 1180 recorded pellagrins of Spartanburg County up to 1915 is shown in Table I. The average indicated death-rate, 15.8 per cent., is not very different from that of the later years. It may be regarded as an approximate indication of the death-rate in the first attack of pellagra.

The relationship between death-rate in the initial attack and the race, age and sex of the patients has been studied in these same

statistics. This death-rate in the 1027 white pellagrins was 12 per cent. and in the 153 negroes it was 41.8 per cent. Searcy's earlier report showed a death-rate of 64 per cent. in pellagra among the colored insane. Lavinder's statistics for Mississippi up to 1913 showed a death-rate of 29.2 per cent. in negroes and 11.4 per cent. in white pellagrins. Pellagra may therefore be regarded as distinctly more fatal to the colored race.

In respect to age and sex the Spartanburg County statistics show 14 cases of pellagra at an age of less than two years, 5 white girls, 8 white boys and 1 colored boy, in the total 1180 cases. Of these only one, the colored boy, died in the first attack. Including these infants there were 212 cases in children under twelve years, 99 white boys, 104 white girls, 1 white child of unknown sex, 2 colored girls and 6 colored boys. Of these there died in the initial attack 2 white boys, 3 white girls and 2 colored boys, a total of 7, or 2.5 per cent. In the age period twelve to sixteen years there were only 21 initial attacks of pellagra, 9 in white girls, 11 in white boys and 1 in a colored girl aged fifteen years. Only one of these died in the year of onset, a white girl, aged thirteen years. The low incidence of pellagra in these four years is in marked contrast to the incidence in younger persons of both sexes and to that in older women. In the age period sixteen to twenty years the death-rate in initial attack was 6.7 per cent. in 45 white women, zero in 6 white men, 46.7 per cent. in 15 colored women and 50 per cent. in 2 colored men. The analogous death-rate in each decade after age twenty is shown in Table II. From this table it is evident that pellagra is much more

TABLE II.—DEATH-RATE IN YEAR OF ONSET BY DECADES AFTER AGE TWENTY YEARS.

Decade.	20–29.	30–39.	40–49.	50–59.	60–69.	70–79.	80–89.	Total.
White women .	4.6	9.8	14.9	31.8	47.6	33.3	..	11.9
White men . .	16.7	20.0	15.9	24.5	21.7	37.5	100.0*	21.2
Negro women .	31.0	43.3	63.3	40.0	66.7	..	0.0*	40.2
Negro men . .	33.3	50.0	0.0	50.0	71.4	..	100.0*	50.2

* Only one case in each instance.

fatal in its initial attack in the negro race and in males, precisely those groups least frequently attacked by the disease in the population studied; furthermore there is a clear indication of increased death-rate with increased age. The benign character of the disease in children is especially noteworthy.

The Interval after the Initial Attack. Subsequent to the initial attack the patient may again become quite fit. There is ordinarily a distinct gain in weight and in some a rather striking gain. The patient frequently refuses to believe that his attack could have been any such serious disease as pellagra. In nearly half the cases,

however, there remains even at this time evidence of depressed vitality, weakness, diminished body weight, diminished or absent menstrual flow in women. As a rule the vast majority of pellagrins improve as colder weather comes on and all but a very few appear quite well in the winter. A few remain weak, cachectic or mentally deranged; rarely one continues with diarrhea and cutaneous eruption into the colder season. These latter usually die in December, January or February. Even in a pellagra focus containing hundreds of cases it is ordinarily impossible to demonstrate the characteristic manifestations of the disease in a single case in mid-winter.

The interval of freedom from pellagra may be prolonged indefinitely so that the patient may be considered to have recovered. This is a common result in institutional outbreaks, where a large number of individuals may be attacked at one time and, subsequently, probably as a result of more liberal dietary and improvement in general hygiene of the institution, the disease may promptly and finally disappear.

In the general population of Spartanburg County, 681 pellagrins who survived the year of onset showed 482 with recurrence and 199 free from recurrence the following year, a recurrence rate of 70.8 per cent. Of those who suffered recurrence in the second year 63 died. Of the survivors 292 were followed through the third year, and of them 228, or 78.1 per cent., had recurrences. Of those who survived attacks in the first, second and third years 78.6 per cent. suffered recurrence in the fourth year and in the fifth year the recurrence rate for those with four previous annual attacks was 76.2 per cent. It would appear that when the habit of recurrence has become established it has a strong tendency to continue. On the other hand those who have escaped from recurrence for one or several years may nevertheless subsequently suffer recurrence. Thus of 137 pellagrins who survived the second year without recurrence, 16 suffered recurrence in the third year, 106 remained free from recurrence and 15 were of uncertain record. Of 62 individuals who had passed two years without recurrence, 11 suffered recurrence in the fourth year of the disease (17.7 per cent.). After three years without recurrence, 13.3 per cent suffered recurrence in the fifth year. Indeed, apparently reliable records in one case indicate a recurrence after nineteen years of freedom from recognizable manifestations of the disease.

It is evident that one should be guarded in stating that any patient has recovered from pellagra. It would appear wiser to speak of the disease as arrested or as quiescent, as is now the rule in tuberculosis.

The Recurrent Attack.—The recurrent attack of pellagra resembles in its clinical features the initial attack. On the average, recurrent attacks appear about two weeks earlier in the season than do the initial attacks of that same year. Recurrences are, on the average, milder than the initial attacks and the death-rate is correspondingly

lower. Thus in the Spartanburg County series the total recorded recurrent attacks number 1053 with 130 deaths, or 12.3 per cent. In the same series the death-rate in initial attack was 15.8 per cent. This observation is contrary to the oft-repeated statement that the prognosis as to life is good in the early stages but bad in the late stages of the disease. It is, however, in accord with the general observation that the severe, fulminant cases of pellagra are more frequent in those places where the disease has recently appeared and are rare in districts where it has been endemic for a long time.

In the Spartanburg County series the total instances of escape from recurrence for a year were 617 and the total number of recurrent attacks 1053, the ratio being approximately 4 to 7. The tendency to recurrence depends to a marked degree upon age and sex. This is shown in Figs. 9 and 10. Of 12 white girls under fifteen years of age, with onset of pellagra in 1911, only 6 were known to suffer recurrence in 1912, 4 in 1913 and 3 in 1914. In

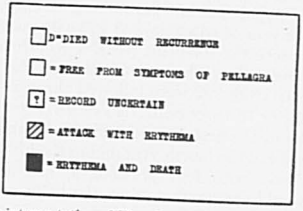

FIG. 8.—Key for interpretation of Figs. 9 and 10. (After Siler, Garrison and MacNeal.)

1914, six remained free from recurrence. Two had passed from observation after 1911 and one had died in 1912 without recurrence of pellagra. The 25 white boys under fifteen years of age with onset of pellagra in the same year show an even more striking recovery rate. Of these 12 escaped recurrence in 1912 while only 8 are known to have suffered recurrence. In 1913 these numbers were 17 and 3 respectively, and in 1914 they were again the same. At the end of four years these 37 children, boys and girls, showed only 6 with known recurrent attack in the fourth year, while 23 escaped recurrence in the fourth year (1914) and 22 were free from signs of the disease in both 1913 and 1914. In the four years there had been only one death in the group, from dysentery, apparently not pellagra. From these and other similar figures it would appear that pellagra is not more serious for children than is measles.

Jobling and Peterson have shown that child pellagrins are of average weight, height and age development until the disease has recurred for some years, when the little pellagrins are somewhat

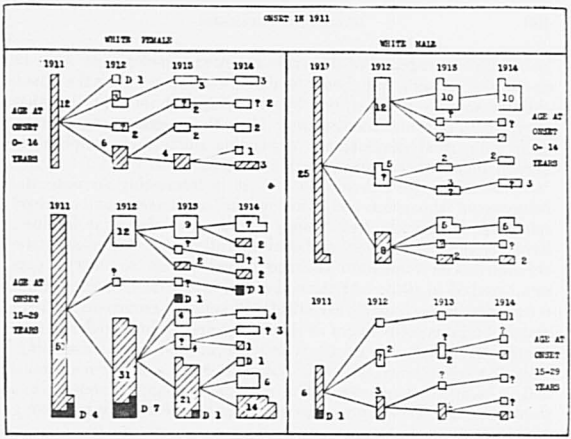

FIG. 9.—Subsequent behavior of white pellagrins of the Spartanburg County series who suffered initial attack in 1911 before attaining the age of thirty years, grouped according to sex and age at onset. Note the absence of deaths in the groups under fifteen years of age and the numerous recoveries in these groups. (After Siler, Garrison and MacNeal.)

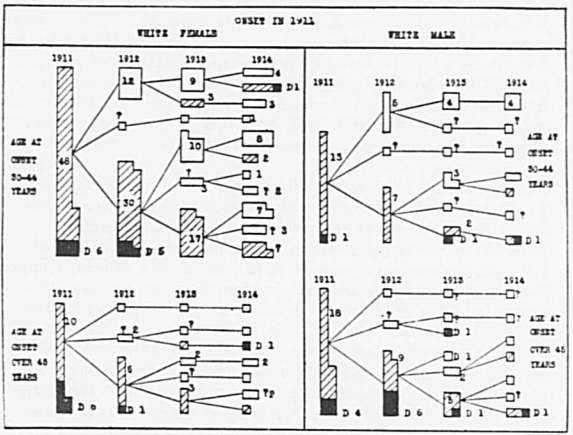

FIG. 10.—Subsequent behavior of white pellagrins of the Spartanburg County series who suffered initial attack in 1911 after attaining the age of thirty years, grouped according to sex and age at onset. Here deaths are more numerous and apparent recoveries less frequent. Note the recurrences after two years of freedom from attack. (After Siler, Garrison and MacNeal.)

below the average. Possibly this retarded development may be due to the pellagra, but there remains also the possibility that these children may be handicapped by some other abnormality, so that they fail to outgrow the disease as does the average normal child, their subnormal development depending upon this complicating abnormality rather than upon the pellagra.

While these children did so well it is interesting to note the behavior of the older pellagrins in the same community, blood relatives of these children, chiefly members of the same families, living in the same houses and eating at the same tables with the children. The women in the age period fifteen to thirty years numbered 55 in 1911. At the end of 1914, 17 were living free from recurrence in the fourth year (1914), 19 suffered recurrence in 1914 and 14 had died of pellagra in the four years. The 7 males in this age group (fifteen to thirty years) are hardly worth discussing. Only 3 were followed in 1914, and of these 2 suffered recurrence and 1 escaped recurrence. The older age groups of both sexes show a similar tendency to recurrence with a death-rate increasing in old age.

Relation to Pregnancy and Childbirth. Pregnant women are relatively less frequently attacked by pellagra, and if the disease appears in them it tends to run a milder course. Thus in our series there were only 20 instances of initial pellagrous attack during pregnancy; 18 recovered, 1 died of pellagra six weeks after parturition and 1 continued in poor health after the child was born in August, 1912, and died of pellagra in September, 1913. Pregnancy bears a similar relationship to recurrent attacks of pellagra. Thus of 79 instances of pregnancy in known pellagrous women, in only 17 instances was a recurrence of pellagra observed during the pregnancy, a recurrence rate of 21.5 per cent. in pregnant women as compared with an annual recurrence rate of 63 per cent. for women in general.

In the months following childbirth women are relatively predisposed to pellagra, both initial and recurrent attacks. In our series 53, or 10.1 per cent., of the pellagrous white women suffered the initial attack of pellagra within six months after the birth of a child. In an analogous manner pellagrous women suffered recurrence of the disease with excessive frequency in the first three months following childbirth, no less than 21, or 24.7 per cent., of the 85 pellagrous white women suffering recurrence in these three months. This rate may be compared with the annual recurrence rate of 63 per cent. by dividing the latter by 4, giving 15.8 per cent. for the average three months period for all women. When the childbirth occurred in the period January to April, inclusive, no less than 50 per cent. of the pellagrous mothers suffered recurrence within three months; when the childbirth occurred in the period September to December all the pellagrous mothers escaped recur-

rence in the following three months. This seasonal relationship should be given attention in the management and care of pregnant women threatened with pellagra.

Pathologic Anatomy. *The Cutaneous Lesions.* Merk has published the most thorough description of the skin lesions as they appear clinically. Unfortunately his work did not include histologic studies. Griffini appears to have been the first to describe the microscopic appearance of the skin. In the desquamative stage he observed a hypertrophic horny layer, with evidence of abundant scaling and excessive productivity in the rete Malpighii. In another case, in the stage of "anemia," he found sclerosis of the bloodvessels of the cutis, more particularly of the papillæ. A third case was examined at the atrophic stage. In this one Griffini found sclerosis of the deeper cutaneous vessels and of the connective tissue of the corium, a frank atrophy of the horny layer and little reproductive activity of the rete Malpighii. The sweat-glands, hair follicles and sebaceous glands seemed not to be abnormal.

P. Raymond studied the skin from the back of the hand of a chronic pellagrin in the atrophic stage. The epidermis as a whole was thinned but the horny layer was thickened absolutely as well as relatively; the papillæ were smoothed out. The horny layer and the rete Malpighii were of equal thickness and the former showed numerous clefts, indicating active desquamation. Hyperkeratosis was a most prominent feature. The stratum granulosum was composed of thin, elongated cells in which eleidin granules could not be distinguished. The rete was atrophic, showing reduction in both number and size of cells. Many of the nuclei had undergone a vesicular degeneration, which Raymond considered to be evidence of irritation in response to vascular dilatation in the corium. The basal cells contained abundant pigment. The papillæ had vanished entirely and the boundary between the ectoderm and the mesodermal layer was represented only by a slightly toothed band. In the corium there were large vascular tufts, the large volume of which contrasted sharply with the atrophic epidermis. The hair follicles, sweat-glands and particularly the nerves were unchanged. The elastic and collaginous fibers appeared normal except for moderate thickening of the latter. In summary, Raymond designates hyperkeratosis and atrophy of the rete as the essential cutaneous changes of pellagra.

Babes and Sion appear to have studied the skin in various stages of the disease. They mention the various features of pellagrous skin lesions, including secondary infections which take place, but these descriptions are inferior to Raymond's in respect to clearness. Babes and Sion mention a moderate diminution in the myelin of the cutaneous nerves as well as the presence of rod-like structures in the corium, suggesting bacteria. They found sebaceous glands containing bacterial colonies and surrounded by granulation tissue,

in which hyperplastic endothelial cells and plasma cells were abundant.

Ormsby and Singer, after study of a large number of sections of pellagrous skin, designate the general picture as that of an angioneurotic process resembling that seen in multiform erythema. They observed thickening of the horny layer, the stratum granulosum and rete being practically normal; edema and cell infiltration

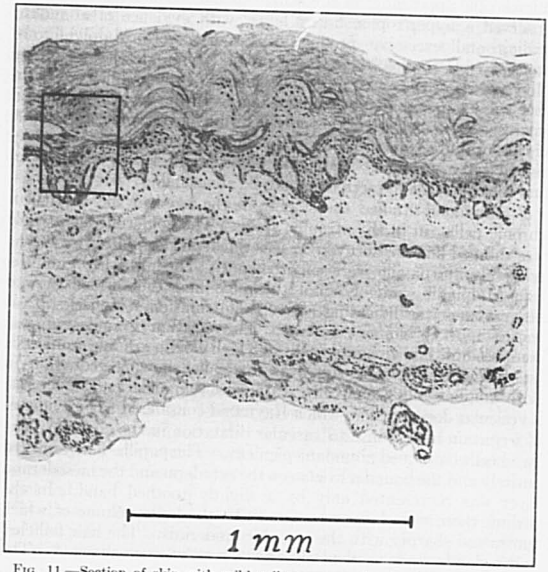

FIG. 11.—Section of skin with mild pellagrous eruption in the stage of hyperkeratosis from a woman aged twenty-nine years; stained with hematoxylin and eosin and drawn with aid of the camera lucida. The horny layer is greatly thickened and shows active desquamation with scattered areas of parakeratosis. There is edema of the corium, especially of the papillary part.

of the superficial part of the corium, especially the pars papillaris. Upon study with the high power the hyperkeratosis was seen to be well marked, with areas of parakeratosis here and there. Many pigment granules were present. The rete was practically normal except in places where its integrity was interfered with by infiltrating cells. In the papillary layer cellular infiltration was quite marked, particularly in the vicinity of bloodvessels. The collagen showed

edematous changes. Deeper parts of the corium appeared normal. No microörganisms were found.

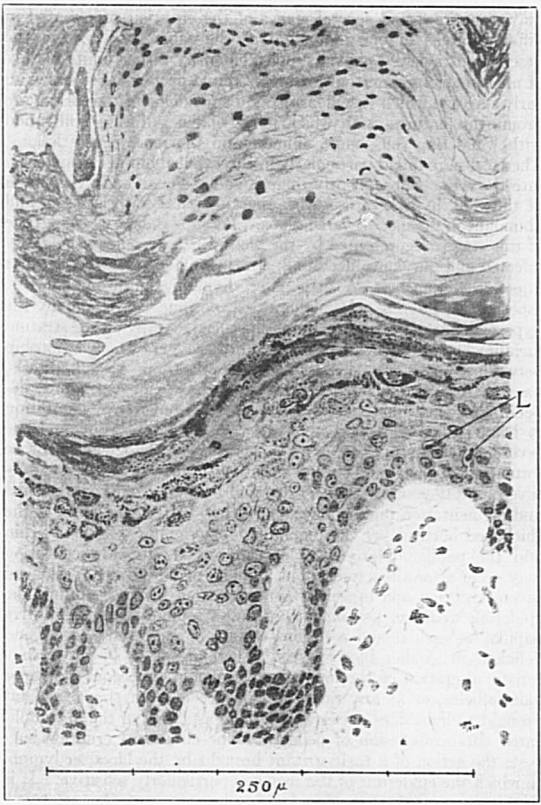

FIG. 12.—A portion of the same section, the location of which is indicated by the black outline in Fig. 11, more highly magnified; camera lucida projection, Zeiss obj. 4 mm., oc. 4. Active desquamation is indicated by the clefts in the horny layer and parakeratosis by the many nuclei in this layer. The stratum lucidum contains numerous brown pigment granules. The regularity of the stratum granulosum is disturbed and the lymph canalicular system of the rete Malpighii is moderately distended by edema. Increase of wandering cells is only slight. At *L* are leukocytes.

An adequate description of the cutaneous lesions of pellagra will require a consideration of all the various stages of the eruption, with a correlation of the gross and microscopic appearances. One may sometimes find several stages of the eruption represented in different areas in one individual at the same time. From the description reviewed above, supplemented by rather limited study of microscopic preparations, it seems to me proper to recognize an early stage, in which vascular injection and edema of the corium are prominent features, with which is associated a diffuse infiltration with wandering cells, more abundant in the more severe lesions. These cells are found particularly in the papillæ, but also wander up into the rete. Subsequently there is added edema and hyperplasia of the rete, hyperkeratosis with spots of parakeratosis, large and abundant in the more severe lesions. Perhaps the most severe type of this stage is represented by the bleb, which becomes secondarily infected and purulent, ulcerated. In the milder forms the vascular injection diminishes. A little later, hyperpigmentation appears, especially in the rete. Hyperkeratosis continues and gradually the hyperpigmentation becomes more superficial, occupying the stratum lucidum and deepest strata of the horny layer. The relationship between congestion, edema, cellular infiltration, hyperkeratosis, parakeratosis and pigmentation is subject to wide variations, depending in part upon individual peculiarities (greater pigmentation in brunettes) and in part upon the rapidity of evolution and the severity of the eruption. An exaggeration of the edema leads to formation of blebs and ulcers, eventually purulent. Less acutely severe eruptions are relatively dry and in these the hyperkeratosis and pigmentation tend to be exaggerated. After exfoliation of the thickened horny layer the remaining epidermis is abnormally thin and the papillæ relatively smoothed out. Complete restitution may occur after a few weeks, but in many instances after prolonged severe eruption and especially after repeated severe eruptions the epidermis remains permanently thin, atrophic, with diminutive papillæ beneath it and a fibrous corium of increased density and deficient in smaller bloodvessels. There seems to be no characteristic alteration of the nerves, sweat-glands, sebaceous glands or hair follicles, or at any rate the evidence of such changes so far brought to light does not establish them as a part of the uncomplicated cutaneous lesion of pellagra. The cutaneous eruption suggests the action of a toxic irritant brought by the blood or lymph, to which the epidermis of the region is particularly sensitive. It is further suggested that this toxic substance may be relatively inactive until it has been changed at the site of the lesion by peculiar ferments of the epithelial cells or possibly by the accessory influence of diffuse or direct sunlight.

The Nervous Lesions. These also require to be considered in relation to the stage of the disease. The earlier observations of

Tuczek would seem to deal rather with the late after-effects of numerous attacks of pellagra if not actually with results of other complicating diseases. More recent studies, particularly those of Mott and of Singer, have brought into prominence the structural changes in the ganglion cells themselves throughout the brain, spinal cord and spinal ganglia. In a rapidly fatal initial attack of

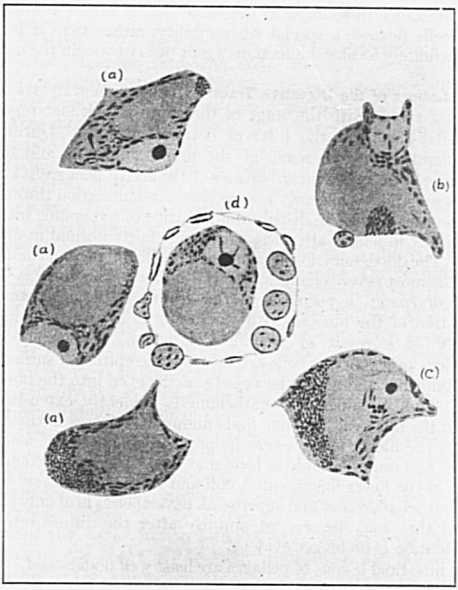

FIG. 13.—Nerve cells showing chromatolysis and pigmentary changes. (*a*) From Clarke's column; (*b*) from anterior central convolution; (*c*) from anterior cornu in cervical region; (*d*) from posterior root ganglion. From a woman, aged forty-three years, dying in the initial attack. (After Singer.)

pellagra, Singer found the most pronounced changes in the Betz motor ganglion cells of the cerebrum and in the cells of Clarke's column in the cord. Fiber degeneration was found diffusely scattered throughout the white matter, not especially involving the pyramidal tracts and not abundant in any tract. Degenerated fibers were also found in both the anterior and posterior spinal roots. The glia cells were perhaps increased around some of the larger

bloodvessels and in places the cerebral vessels showed some increase of adventitial nuclei, but no infiltration of the perivascular sheaths, a striking contrast to the pictures seen in syphilis and in trypanosomiasis. In more chronic cases the increase in glia cells about the bloodvessels was more definite and quite marked in some instances, and the vessels themselves were thickened. The nerve lesions, like the cutaneous changes, indicate the action of a diffusely distributed toxic substance in solution in the blood and lymph, for which the nerve cells possess, a special susceptibility, rather than a formed, more definitely localized infectious agent present within the nervous tissues.

The Lesions of the Digestive Tract. In the alimentary tract also the lesions vary with the stage of the acute attack and represent only after-effects in the interval between attacks. During life the inflammatory hyperemia of the mouth, pharynx and of the rectum are often prominent features of the active pellagrous attack. Autopsy at this stage nearly always shows inflammation throughout the intestine, patchy in distribution. Strips of hyperemic intestine several feet in length alternate with strips fairly normal in appearance. The duodenum, lower ileum, caput coli and rectum commonly show the most severe changes. In the earlier lesions there is vascular engorgement, hyperplasia of the lymphoid tissue, edema and infiltration of the mucosa with wandering cells. In later lesions, possibly as a result of secondary infection, moderately dense collections of wandering cells extend from the epithelial surface into the submucosa and along the vessel sheaths even into the muscular coats. Loss of superficial epithelium is evidently extensive, for even in the milder lesions one finds numerous mitoses in the crypts and, in the older, more severe lesions the glands are deficient in number and quite variable in form and size. Ulceration commonly occurs in the lower ileum, caput coli and rectum, and these ulcers, which are small, round and superficial, nevertheless heal only slowly, so that they may be seen at autopsy after the diffuse intestinal inflammation is no longer evident.

The intestinal lesions of pellagra are least well understood. Some authorities (Roussel) regard them as entirely trophic and dependent upon antecedent changes in the nerves. Others regard them as an expression of direct toxic action on the intestinal wall by the essential poison of pellagra during its absorption. Doubtless the normal intestinal microörganisms also play a part, particularly after ulceration has occurred. A clear understanding of the intestinal lesions will doubtless have to await a better understanding of the etiology of pellagra itself.

Pathologic Chemistry. Myers and Fine found the gastric juice of pellagrins often deficient in hydrochloric acid and not infrequently in pepsin also. The feces contain, as a rule, a markedly abnormal excess of indol and skatol. The urine commonly shows a

trace of albumin and a few tube casts and in most cases a distinct test for indican. At times indican is present in enormous amount. These findings all point to a gastro-intestinal derangement and profound bacterial decomposition in the intestine. Metabolism studies on pellagrins have shown that these patients possess normal ability to utilize the food principles. In fact the utilization was surprisingly high, considering the evidence of local gastro-intestinal derangement.

Bacteriology. The work of Tizzoni and his associates, who have isolated an organism from the blood which they regard as the cause of pellagra, may probably be dismissed as unreliable. The intestinal flora is certainly profoundly altered in pellagra. There is a large increase in the variety of microbes present in the feces as compared with the normal as well as a disturbance in the numerical relationships of the normal types. Further investigations in this field of work are much to be desired.

Diagnosis. The diagnosis of pellagra has to be made by observation of the symptoms and signs presented by the patient, and this diagnosis may be supported by demonstration of the typical anatomic changes in the tissues. Accessory facts may be utilized to some extent. Of these, perhaps the most important is a history of having lived in a pellagrous district. Some authors attach great importance to a history of having eaten maize, even going so far as to exclude pellagra absolutely if maize has not been eaten (Roussel) or even to assume that all persons who habitually eat maize actually suffer from pellagrous intoxication in a mild form. These conceptions are not in accord with observations on pellagra in the United States. Some authors appear to attach considerable importance to emaciation and physical weakness as evidence of pellagra, but these manifestations are common to so many pathologic conditions that comment upon their diagnostic value is superfluous.

Among the signs and symptoms, only the typical cutaneous eruption on the backs of the hands warrants a definite diagnosis of pellagra. This eruption bears the same relation to the diagnosis of pellagra as does the eruption of smallpox or measles to the diagnosis of those diseases. In the recognition of the pellagrous eruption, its localization on the backs of the hands, approximate bilateral symmetry, sudden appearance as an erythema, gradual evolution to hyperkeratosis, with or without hyperpigmentation, the subsequent desquamation and final restitution are important. A dermatitis due to molds may simulate this eruption in appearance, but such a dermatitis usually occurs elsewhere than on the backs of the hands. Roussel, however, mentions cases in which the differential diagnosis was finally made only by the microscopic demonstration of mycelial threads in lesions on the backs of the hands. The beginning and developmental course of a mold derma-

titis is usually different also, so that continued observation may alone suffice for its recognition.

A tentative diagnosis of pellagra is often justified without observation of the eruption. Certainly the disease is usually still present after the acute attack and the eruption have disappeared and there is abundant evidence that the patient suffers from the disease in the absence of the eruption. However, such a tentative diagnosis should be abandoned if the patient does not subsequently present the eruption or confess to its earlier presence.

Prophylaxis. The practical prevention of pellagra has to be based upon a knowledge of etiology. The measures may be grouped in two classes: (1) Those measures which enhance the individual resistance to the disease, and (2) those which diminish or exclude the opportunity for the causative factor or factors to attack the individual. First, in regard to individual resistance: it is evident that even in its endemic centers pellagra attacks only a small proportion of the population at any one time. Those who are physically vigorous escape to a very large extent and therefore the maintenance of robust physical vigor is an excellent insurance against pellagra. The nature of human existence, however, is such that in every natural community of families there will be some tender young children, some children occasionally sick with measles, whooping-cough or gastro-intestinal derangement, some women in the puerperium and some old people in the decline of life when robust vigor naturally wanes. Therefore, although the maintenance of individual resistance at a high level offers much, it nevertheless has its limitations. In regard to the second class of measures, which diminish the opportunity for the cause to reach the individual, opinion is much less settled. Most effective is distance from persons suffering from the disease. When pellagra has prevailed among the general population new cases may be expected to continue to appear. In the United States the disease numbers its victims by the thousands every year in some states while in others it is either wholly unknown or is recognized as a rare disease of transient visitors from pellagrous districts. Even in its endemic areas, large districts remain relatively free from the disease while in other parts from 5 to 10 per cent. of the people are pellagrins. Avoidance of the endemic centers becomes, therefore, an evident means of avoiding pellagra. However, even in the small villages most severely afflicted, those people who live farther away than next door from the residence of a pellagrin are less liable to contract the disease than those who live next door to or in the same house with such sick persons.

Sanitary disposal of the human wastes of a community would appear to be one of the most important factors in preventing the occurrence of new cases of pellagra. Physical equipment such as sewers, a piped water supply and screens are evidently important,

but sanitary instruction, and especially adequate inspection service to insure the proper use of the equipment, must not be neglected. Lunatic asylums, provided throughout with the most approved sanitary appliances, still have their "untidy wards."

General improvement in nutrition, and particularly the liberal consumption of milk and of wholesome, fresh meat, certainly plays an important part in preventing pellagra, not alone among those who have not yet contracted the disease but also in preventing recurrences in those already affected by it. It is probable that such foods act by enhancing the general vigor and thus increasing resistance of the individual to the disease, but many investigators believe that these foods have a more definitely specific action by relieving a supposed specific deficiency or supplying a necessary vitamine in the diet.

Treatment. The treatment of pellagra offers two phases for consideration: (1) The management of the case during the acute attack of the disease, and (2) the management of the patient after recovery from the attack. As we have seen, recovery from the attack occurs in about 85 per cent. of instances. In fact, about half the attacks do not cause the patient to go to bed and the vast majority run their course to recovery without any definite treatment. In those who do become bedridden the death-rate is fairly high.

Bearing in mind, therefore, that the attack tends to self-limitation the indications are for supportive and symptomatic treatment. A comfortable bed in a clean, pleasant and moderately cool room, with a competent, interested and sympathetic nurse, almost ensure recovery. The lips, mouth, teeth and pharynx should be kept scrupulously clean. Irritation of the eruption is lessened by bandaging with an ointment of zinc oxide, lanolin and vaselin. The diet should be liberal and should include milk as the principal element. Every effort should be made to encourage the appetite, but overfeeding to the point of distaste or nausea is dangerous. In severe cases food may sometimes be refused entirely for as long as three days, with subsequent return of appetite and eventual recovery. Pellagrins are very susceptible to suggestion and the presence of recovered patients has a real therapeutic value. Conversely, a pellagrin, surrounded by friends or by nurses who regard the disease as horrible and necessarily fatal, usually dies. Probably the psychical state influences directly the nutrition and indirectly the outcome of the attack.

Pustules, fissures, ulcers and extensive sloughs of the skin require mild antiseptic wet dressings. The diarrhea had best not be intefered with, and it is not a contra-indication to a liberal milk diet. Peripheral neuritis and paresis require massage, passive movements and elevation of the bed-clothing from the feet in chronic bedridden cases. Mental derangement should be expected in all severe cases, and it requires intelligent, sympathetic treatment.

Physical restraint usually aggravates the difficulty. Of the hypnotics, probably chloral is most effective and least objectionable. Morphin is not recommended. Mental cases require vigilance, for there is a real suicidal tendency in some. The noisy delirium of these patients makes their treatment in a general hospital very difficult.

Complicating disorders should be carefully looked for. Often their importance quite overshadows that of the pellagra itself. In a tuberculous pellagrin treatment of the tuberculosis is the pressing indication. Chronic alcoholism and its sequelæ, and, in women, pelvic disease, are common complications of pellagra and require their special consideration. In institutional pellagra, undernourishment from prolonged lack of adequate food is common, and it is one of the most easily corrected complications.

After recovery from the attack every effort should be made to prevent recurrence by increasing the general resistance of the patient and by adequate treatment of any debilitating disorder, particularly those just mentioned. Relief from overwork, administration of tonic drugs and especially removal to a cooler climate are to be recommended. Particular efforts should be made to retain the resistance and the nutrition of the patient at a high level during the spring and early summer of the following year because of the danger of recurrence at this time. Public charity may do much to better the resistance of poverty-stricken pellagrins, but it sometimes happens that the particular handicap of the patient cannot thus be relieved, and this is especially true of those pellagrins who are already in comfortable financial circumstances. Such patients may require a careful study of their general condition and a careful regulation of their lives for a period of several years.

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THE ABSENCE OF PANCREATIC SECRETIONS IN SPRUE AND THE EMPLOYMENT OF PANCREATIC EXTRACT IN THE TREATMENT OF THIS DISEASE.

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Our ideas of sprue as a clinical entity date from the works of Manson, Vander Burg and Fayrer in the '80s, although it has been recognized since 1737, and Hillary clearly defined it in 1766. Manson described it as a disease of the tropics, characterized by "a peculiarly inflamed, superficially ulcerated, exceedingly sensitive